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(Article begins on next page)

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Increased Epithelial Gaps in the Small Intestine Are Predictive of Hospitalization and Surgery in Patients With Inflammatory Bowel Disease

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OBJECTIVES: Epithelial gaps resulting from intestinal cell extrusions can be visualized with confocal laser endomicroscopy (CLE) during colonoscopy and increased in normal-appearing terminal ileum of inflammatory bowel disease (IBD) patients. Cell-shedding events on CLE were found to be predictive of disease relapse. The aim of this study was to assess the prognostic value of epithelial gap densities for major clinical events (hospitalization or surgery) in follow-up.

METHODS: We prospectively followed IBD patients undergoing colonoscopy with probe-based CLE (pCLE) for clinical events including symptom flares, medication changes, hospitalization, or surgery. Survival analysis methods were used to compare event times for the composite outcome of hospitalization or surgery using log-rank tests and Cox proportional hazards models. We also examined the relationship of gap density with IBD flares, need for anti-tumor necrosis factor therapy, disease duration, gender and endoscopic disease severity, and location.

RESULTS: A total of 21 Crohn's disease and 20 ulcerative colitis patients with a median follow-up of 14 (11–31) months were studied. Patients with elevated gap density were at significantly higher risk for hospitalization or surgery (log-rank test $P = 0.02$). Gap density was a significant predictor for risk of major events, with a hazard ratio of 1.10 (95% confidence interval = 1.01, 1.20) associated with each increase of 1% in gap density. Gap density was also correlated with IBD disease duration (Spearman's correlation coefficient rho = 0.44, $P = 0.004$), and was higher in male patients (9.0 vs. 3.6 gaps per 100 cells, $P = 0.038$).

CONCLUSIONS: Increased epithelial gaps in the small intestine as determined by pCLE are a predictor for future hospitalization or surgery in IBD patients.

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INTRODUCTION

Altered intestinal permeability has been implicated in the pathogenesis of inflammatory bowel disease (IBD).[1,2] Increased gut permeability has been well demonstrated in patients with Crohn's disease (CD) and their first-degree relatives,[3,4] and appears to predict impending disease relapse.[5] Changes in tight-junction protein expression in active CD patients[6] and correlation of colitis severity with alterations of intestinal permeability in rodent models[7,8] further support the notion that barrier dysfunction has an important role in the development of IBD. The barrier function of the intestinal epithelium is maintained by epithelial cells and tight junctions in between cells, allowing absorption of nutrients while preventing undesirable solutes, microbes, and antigens from entering the body.[9,10] Stem cells in the base of crypts produce new epithelial cells that mature and migrate to the top of the intestinal villi, where they are eventually shed.[11] In rodent studies, extrusion of an intestinal epithelial cell leaves a gap or discontinuity in the epithelium that may take up to 12 min to resolve, and may potentially compromise the barrier function.[12] Increased cell shedding induced by tumor necrosis factor (TNF) has been shown to result in barrier dysfunction in the intestine.[13] In patients, these epithelial gaps can be observed using confocal laser endomicroscopy (CLE) with administration of fluorescein.[13,14] CLE is a novel endoscopic imaging modality investigated for a number of indications in IBD, including classification of mucosal inflammation,[15] detection of intramucosal neoplasia,[16,17] and identification of epithelial gaps in the small intestine after cell extrusion.[13,14] We have previously found an increased density of epithelial gaps in the small intestine of IBD patients.[18] Recently, epithelial gaps and cell-shedding events observed using CLE were shown to be predictive of disease relapse in IBD patients.[19]

A major challenge in the management of IBD patients is that the clinical course of disease can be highly variable.[20] There is

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little correlation between clinical activity, biological parameters, and endoscopic severity in CD patients.[21,22] A number of clinical and laboratory parameters were previously reported to be associated with poor clinical outcome: young age at time of diagnosis,[23] male gender,[24] smoking status,[25] peri-anal disease,[23] perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)/anti-*Saccharomyces cerevisiae* antibodies (ASCA) titer,[26,27] C-reactive protein (CRP),[28,29] pancolitis,[30,31] presence of primary sclerosing cholangitis,[25,32] and granuloma.[33] Endoscopic finding of mucosal healing,[32] particularly after administration of anti-TNF therapy, is predictive of favorable clinical outcome,[34,35] whereas lack of mucosal healing on therapy is associated with a more aggressive disease course.[36] Endoscopic indices are increasingly used to determine the efficacy of various therapeutic agents for IBD, with mucosal healing considered to be important in predicting disease outcome, including colectomy in ulcerative colitis (UC) and surgery and hospitalization in CD. We hypothesize that increased intestinal cell extrusion (measured as an increased epithelial gap density) is a surrogate marker for barrier dysfunction in IBD, and thus may have predictive value for clinical disease course and outcomes. In our previous study,[18] a retrospective review of disease course before colonoscopy with probe-based CLE (pCLE) revealed a possible relationship between the epithelial gap density and major clinical events (hospitalization or surgery) in the year preceding pCLE.

The aim of this study was to assess the predictive value of epithelial gaps for major clinical events (hospitalization or surgery) in IBD patients undergoing colonoscopy. We also examined the relationship of epithelial gap density with respect to disease duration, gender, number of flares in the follow-up period, and endoscopic disease severity and location.

METHODS

This was a prospective, double-blinded, observational cohort follow-up study of IBD patients undergoing pCLE of the terminal ileum during standard-of-care colonoscopy. Patient enrollment was from March 2009 to November 2010, with the follow-up period ending in October 2011. We recruited more UC patients in addition to patients from our study on epithelial gap density in IBD[18] and a pilot study in CD[14] based on our sample size calculation for follow-up. The study was registered at ClinicalTrial.Gov (NCT00988273). The study protocol was reviewed and approved by the Human Ethics ResearchReview Board at the University of Alberta, Edmonton, Alberta, Canada. The study group consisted of patients with known or newly diagnosed IBD undergoing colonoscopy for clinical indications (evaluation of symptoms or cancer surveillance). The inclusion criteria for the study were age over 18 years and the ability to give informed consent. Exclusion criteria included having known allergies to fluorescein or shellfish, impaired renal function (serum creatinine over 1.5 mg/dl) or being pregnant or nursing patients. All patients gave written informed consent to participate in the study. The disease status of patients undergoing colonoscopies was classified as active disease (evaluation of symptoms) or inactive disease (asymptomatic patients undergoing cancer surveillance). Patient demographics, history, physical examination findings, and endoscopic findings were recorded in a database.

All patients successfully underwent colonoscopy with intubation of the terminal ileum, at which time 5 ml of 10% fluorescein solution was administered intravenously. Confocal images of the terminal ileum were obtained with the ultra-high-definition pCLE probe (UHD Coloflex, Mauna Kea Technologies, Paris, France) following a previously reported protocol.[18] Frame-by-frame confocal images of normal-appearing terminal ileum at about 10 cm proximal to the ileocecal valve were collected and digitally stored for analysis. pCLE imaging was limited to areas of endoscopically normal mucosa in the terminal ileum. Review and analysis of pCLE images were conducted in a *post-hoc* manner as previously described.[18] In brief, pCLE images were blindly examined by two reviewers for the selection of adequately imaged villi, defined as villi with at least 75% surface area visualized on the pCLE image, with at least three different consecutive views of the villi seen. Epithelial cells and gaps were manually counted in the villi and the highest frequency of epithelial gaps for any individual patient was used to determine the gap density (range: 3–10 villi evaluated per patient). The gap density was calculated as the number of epithelial gaps per 100 epithelial cells counted in the adequately imaged villi. Normal gap density was defined as $\leq$6%, which was the estimated 95th percentile of the control population from our previous study.[18]

Patient outcomes in the follow-up period after colonoscopy with pCLE were tracked by a review of electronic medical record systems for flares, hospitalizations, surgeries, and medication changes. The province of Alberta has successfully implemented a single, province-wide Electronic Health Record (EHR)—Alberta Netcare. It is a database that encompasses all inpatient visits, emergency room visits, laboratory investigations, radiologic tests, endoscopic procedures, surgeries, and hospitalizations within the province of Alberta (http://www.albertanetcare.ca). Regardless of the location of health-care delivery, the electronic medical record can be accessed. The electronic medical record system also tracks medication profiles and refills at most pharmacies within the province of Alberta. The outpatient medical records for all enrolled study patients are stored in the University of Alberta Division of Gastroenterology electronic medical database (Wolf Medical system), where all clinic visits are recorded, including letters to and from referring primary-care physicians. Flares in IBD patients were defined as symptomatic changes requiring office visits, including but not limited to increased stool frequency, reduced stool consistency, or presence of blood in stool. For Crohn's patients, this represented an increase in the Harvey–Bradshaw index of $>$2, and for UC patients, an increase of 2 in the partial Mayo UC score. IBD-related surgeries in the follow-up period were recorded for indications for surgery, type of surgery, and any complications from the surgeries. For hospitalization, the indications and number of hospitalizations were recorded. If a patient had one hospitalization or surgery, it was counted as one major event. Multiple admissions or surgeries for the same patient were counted as one major event.

The primary-study end point was the cohort comparison of the IBD-related hospitalization or surgery in patients with

normal and elevated epithelial gap density as determined by pCLE. Both clinicians and patients were blinded to the result of pCLE and thus all treatment decisions regarding patient management were made independently of pCLE results during the follow-up. For secondary analyses, we investigated the association between epithelial gap density and duration of disease to determine if excess cell extrusion increased with longer duration of disease. We also examined whether epithelial gap density correlated with the number of flares in the follow-up period. The correlation of gap density with endoscopic location and severity of disease was also studied. Finally, we looked at epithelial gap density and its relationship with gender, systemic inflammatory markers (CRP levels), and the need for anti-TNF therapy.

Statistical analysis

Sample size calculation. For the cutoff for abnormal gap densities, we defined gap density values $>6\%$ (the estimated 95th percentile of the control population) to be abnormal. On the basis of our previous study examining the retrospective clinical course of patients undergoing pCLE (23% vs. 60% hospitalization or surgery in the year proceeding pCLE), we assumed median event-free survival times, with respect to the primary outcome, of 32 and 9 months for patients with normal and elevated epithelial gap density, respectively. To attain a statistical power of 0.80 with an alpha of 0.05, and assuming an accrual period of 18 months with an additional 12 months of follow-up, a total of 38 patients were needed for this study, assuming equal numbers of patients in each group. Sample size calculations were conducted using PS (Version 3.0, 2009, Vanderbilt University, Nashville, TN, USA).

The primary end point of the study was a composite variable of IBD-related hospitalization or surgery in the follow-up period. Continuous variables that were normally distributed were expressed as mean ± s.d., whereas non-normally distributed continuous variables were expressed as median (range). Event-free survival probabilities were estimated by the Kaplan–Meier method and the comparison between patients with normal and elevated gap densities was conducted via the log-rank test. The Cox proportional hazards model was used to assess gap density as a continuous predictor for the risk of major clinical events. Two-sided P values of <0.05 were considered to be significant. For secondary analysis, we assessed the relationship between epithelial gap density and other outcomes of interest using appropriate non-parametric tests. The relationship between epithelial gap density and ordinal outcomes (years since diagnosis, number of flares, disease severity, and CRP levels at the time of colonoscopy) were assessed with the Spearman rank correlation coefficient. When assessing the relationship between gap density and binary outcomes (gender, need for TNF agents), the Wilcoxon rank sum test was used. When assessing the relationship between gap density and nominal outcomes (disease location), the Kruskal–Wallis test was used. All analyses were conducted using the STATA data analysis and statistical software (StataCorp LP, College Station, TX).

Table 1 Baseline patient characteristics

	Crohn's disease ($N=21$)	Ulcerative colitis ($N=20$)
Age (years), mean ± s.d.	37.2 ± 14.5	45.0 ± 15.5
% Male	48	55
Disease duration (years), median (IQR)	6 (0–17)	3 (0.75–11)
Endoscopic disease location (%)		
Ileal	9 (43)	
Ileocolonic	5 (24)	
Colonic	7 (33)	
Pancolitis		12 (60)
Left side/proctitis		8 (40)
Endoscopic disease severity (%)		
Normal	2 (10)	4 (20)
Mild	11 (52)	11 (55)
Moderate	5 (24)	5 (25)
Severe	3 (14)	
Medications (%)		
No therapy	8 (38)	6 (30)
Aminosalicylate	4 (19)	11 (55)
Steroids	2 (10)	3 (15)
Immunomodulator	6 (29)	4 (20)
Biologics	3 (14)	0 (0)
C-reactive protein, median (IQR)	5.5 (1.8, 14.2)	2.9 (2.3–15.4)

IQR, interquartile range.

RESULTS

Baseline study patient characteristics. The baseline study patient characteristics are shown in Table 1. There were 41 IBD patients (21 CD and 20 UC) in the study with a median follow-up of 14 (5–31) months. Study patients included those from our pilot study (7 CD and 1 UC) and 26 patients from our prospective IBD gap density study who remained in Alberta for the follow-up period (14 CD and 12 UC), and an additional 7 UC patients. Indications for colonoscopy in the 41 patients were: evaluation of symptoms in 27 (15 CD and 12 UC) and cancer surveillance in 14 (6 CD and 8 UC). The age, gender, disease duration, and serum CRP levels were comparable between CD and UC patients. The median follow-up period for CD patients was longer than that for UC patients (14 vs. 18.5 months, $P=0.01$). Follow-up data were available for all study patients. Multiple hospitalizations or surgeries in the same patient were counted as one event for the primary outcome analysis, and the time to first event was used for analysis. The median follow-up for patients with elevated gap density was longer than that for patients with normal gap density (13 vs. 17 months, $P=0.02$).

Correlation of epithelial gap density and rate of hospitalization or surgery. Patients with normal gap density were found to be at lower risk for events (hospitalization or surgery) than those with elevated gap density ($P=0.02$ from log-rank test) during the follow-up period, shown in Figure 1. Using Cox proportional hazards analysis, gap density was found to be a significant predictor for risk of events, with a hazard ratio of 1.10 (95% confidence

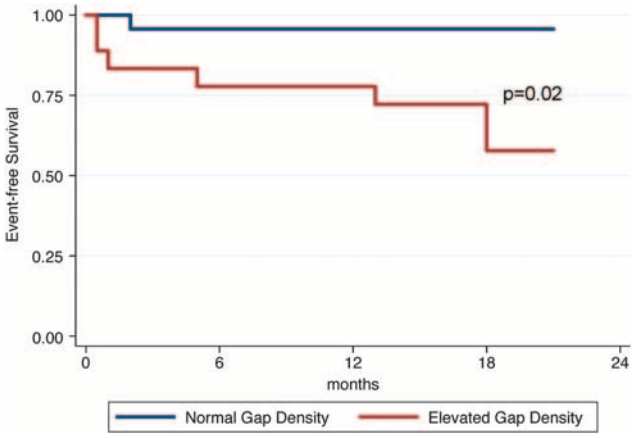

Figure 1 Kaplan–Meier plot of event-free survival probabilities in inflammatory bowel disease (IBD) patients with normal and elevated gap densities following probe-based confocal laser endomicroscopy.

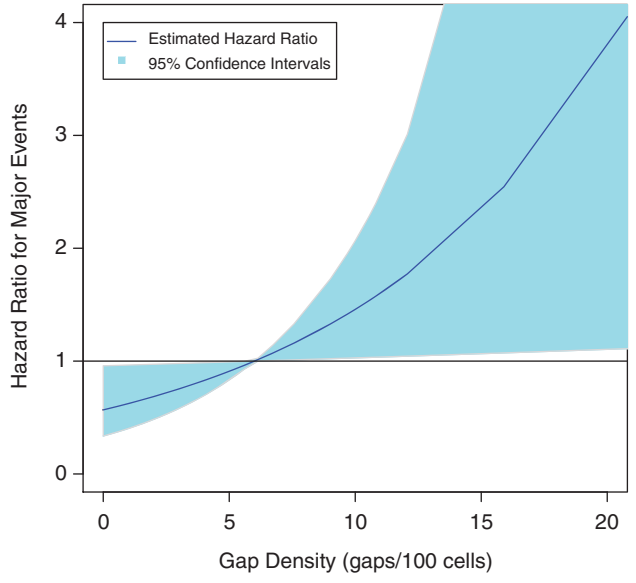

Figure 2 Hazard ratio associated with epithelial gap density as a continuous predictor from the Cox proportional hazards model ($P = 0.034$).

interval = 1.01, 1.20) associated with each increase of 1% in gap density, shown in Figure 2. Whether the patient had active or inactive disease at the time of colonoscopy was not predictive of the need for hospitalization or surgery in follow-up. In all, 3 of the 14 (21%) IBD patients undergoing surveillance colonoscopy had a major event, whereas 4 of 27 (15%) patients undergoing colonoscopy for symptomatic evaluation had a major event in the follow-up period.

Correlation of epithelial gap density and IBD flares. In the 34 remaining patients who did not have a major clinical event in the follow-up period, 10 had symptomatic flares (29%). Epithelial gap density was marginally correlated with the number of flares in the follow-up period, with a Spearman rank correlation coefficient (ρ) of 0.27 ($P = 0.08$). Flares were successfully managed by gastroenterologists in an outpatient

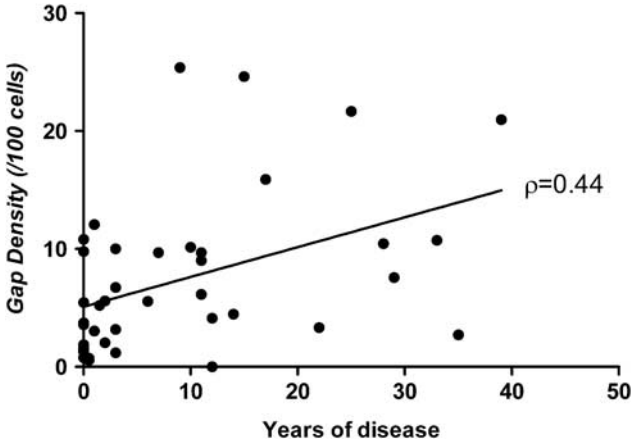

Figure 3 Distribution of intestinal epithelial gap densities as a function of disease duration for inflammatory bowel disease (IBD) patients. Epithelial gap density is expressed as the number of epithelial gaps per 100 cells counted. $P = 0.004$.

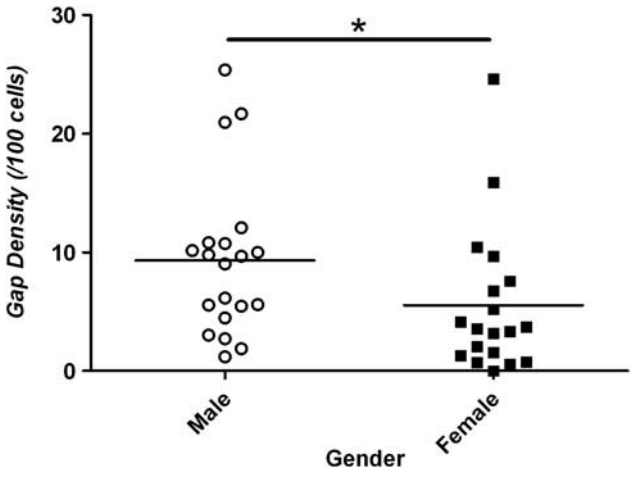

Figure 4 Comparison of epithelial gap density of the small intestine for male and female inflammatory bowel disease (IBD) patients. *$P = 0.038$.

setting. Two patients were treated with dose escalation of existing medical therapy, whereas others required step-up therapy to immunomodulators or anti-TNF therapy. There was no correlation between anti-TNF therapy initiation and epithelial gap density ($P = 0.28$).

Correlation of epithelial gap density and other clinical parameters. We examined the relationship between epithelial gap density and the following clinical parameters: duration of IBD, endoscopic disease severity and location, CRP level at the time of colonoscopy, and gender. We found a significant positive correlation between epithelial gap density and the duration of IBD (years since diagnosis), with a ρ of 0.44 ($P = 0.004$), shown in Figure 3. Male IBD patients also appeared to have a higher median epithelial gap density compared with female IBD patients: 9.0 vs. 3.6 gaps per 100 cells counted ($P = 0.038$), shown in Figure 4. No significant relationships were found with endoscopic disease severity or location, and CRP levels.

DISCUSSION

In this study, we found that the density of epithelial gaps in the terminal ileum of IBD patients as determined by pCLE was predictive of the need for hospitalization or surgery during follow-up. This finding supports our hypothesis that excess epithelial cell extrusion in IBD (measured as an increased epithelial gap density) serves as a surrogate marker for mucosal barrier dysfunction, thus having a prognostic value for clinical course of disease. Consistent with a recent report that barrier dysfunction from cell extrusion is predictive of disease relapse,[19] our results indicate that gap density, a semi-quantitative measure of cell extrusion, is a linear predictor for future major events such as hospitalization or surgery in IBD.

Endoscopic findings associated with aggressive IBD include deep and extensive ulcerations and lack of mucosal healing,[36] particularly after administration of anti-TNF therapy.[34,35] Based on experience from the past few years, some of the new therapeutic goals for IBD treatment are steroid-free remission, mucosal healing, and reduction in hospitalization and surgery.[37] Hospital admission and surgery is associated with increased morbidity and mortality for patients, and significant costs.[38] Therefore, delineation of the predictors for IBD patients at high risk for major events during their colonoscopy would be valuable. Recently, local barrier dysfunction identified by the Watson grade of cell shedding and the presence of fluorescein leakage and micro-erosions on CLE was shown to be predictive of relapse in IBD.[19] Consistent with their findings, our study results indicate that the epithelial gap density, a semi-quantitative measure of barrier disruption in the epithelial lining, can identify patients at risk for a more severe disease course, that is, the need for IBD-related hospitalization or surgery.

The positive correlation observed between epithelial gap density and disease duration in IBD indicates that excess epithelial cell extrusion, either as a cause or as a result of the disease process, appears to be increased with longer duration of disease. This is consistent with the observation that young age at diagnosis is associated with more aggressive disease for both CD and UC patients. Interestingly, the endoscopic location of disease did not correlate with gap density in Crohn's patients, that is, patients with ileitis did not have elevated gap density in normal-appearing areas of the terminal ileum. Epithelial gap density in the terminal ileum appeared not to be influenced by the presence of disease in the immediate surrounding areas. Epithelial gap density also did not correlate with systemic CRP levels, suggesting that epithelial cell extrusion is mediated by events at the mucosal level rather than by systemic inflammation.

We found a marginal correlation between epithelial gap density and the number of relapses in the follow-up period. In addition, the gap density correlated with the duration of disease in IBD patients, supporting a potential role of epithelial barrier dysfunction in the pathogenesis of IBD. In the current study, we did not find a relationship between epithelial gap density and endoscopic severity or location of disease. We did find that male IBD patients appeared to have higher gap densities than female patients. In a recent study, male gender was identified as an independent risk factor for the development of complications in CD,[24] whereas other studies suggest that women appeared to be at higher risk for intestinal resection and surgery in CD.[20,23,39] Future large, prospective studies are needed to clarify the effect of gender on clinical outcomes.

IBD is a chronic disease and most patients will experience flares. A recent prospective longitudinal study conducted in Norway reported a cumulative relapse rate of 90% in CD patients.[20] It is important to be able to identify a subgroup of patients at risk for serious flares requiring hospitalization or surgical management. Although our study results are preliminary, it appears that a higher gap density is predictive of more severe clinical disease. A higher gap density may reflect increased epithelial cell shedding induced by enhanced TNF-α and other proinflammatory cytokine activities. It remains to be determined how this impacts disease management.

There are several limitations to our current study. This is a relatively small study of 41 patients, and our results will need to be confirmed in larger, multi-centered studies of gap density determination in IBD patients. The follow-up period is longer for CD compared with UC, as many UC patients were recruited at a later time, despite the difference in follow-up time, we still found a significant relationship between elevated gap density and major clinical events using a log-rank test, stratified by disease status. Although we observed a marginal relationship between epithelial gap density and the number of flares in the follow-up period, our study was not designed to evaluate this end point, and may be underpowered to ascertain a significant relationship.

In conclusion, we show that the epithelial gap density in the terminal ileum, as determined by pCLE during colonoscopy, is a predictor for aggressive clinical disease in IBD. CLE evaluation of the terminal ileum during colonoscopy may enable clinicians to further risk stratify IBD patients.

CONFLICT OF INTEREST

Guarantor of the article: Julia J. Liu, MD, MSc.
Specific author contributions: Study design; analysis and interpretation of data; funding; and study supervision, drafting of the manuscript; critical revision of the manuscript for important intellectual content: Jean-Francois Turcotte; acquisition of data; critical revision of the manuscript for important intellectual content: Karen Wong; analysis of data; and critical revision of the manuscript for important intellectual content: Stephanie J. Mah; acquisition of data; critical revision of the manuscript for important intellectual content: Levinus A. Dieleman; acquisition of data; critical revision of the manuscript for important intellectual content: Dina Kao; acquisition of data; critical revision of the manuscript for important intellectual content: Karen Kroeker; statistical analysis; critical revision of the manuscript for important intellectual content: Brian Claggett; study concept and design; critical revision of the manuscript for important intellectual content: John R. Saltzman; analysis of data; critical revision of the manuscript for important intellectual content: Eytan Wine; study concept and design; critical revision of the manuscript for important intellectual content; and funding: Richard N. Fedorak; study concept and design; acquisition of data; analysis and interpretation of data; funding; and study supervision, drafting

of the manuscript; critical revision of the manuscript for important intellectual content: Julia J. Liu.

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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Epithelial gaps resulting from extrusion of epithelial cells can be visualized in the small intestine in patients using confocal laser endomicroscopy.
- The density of the epithelial gaps in inflammatory bowel disease patients is creased compared to non-IBD controls.

WHAT IS NEW HERE

- In IBD patients, increased epithelial gap density is an endoscopic predictor of aggressive disease.
- Epithelial gap density is correlated with duration of IBD disease, and marginally related to the number of flares in follow up.

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